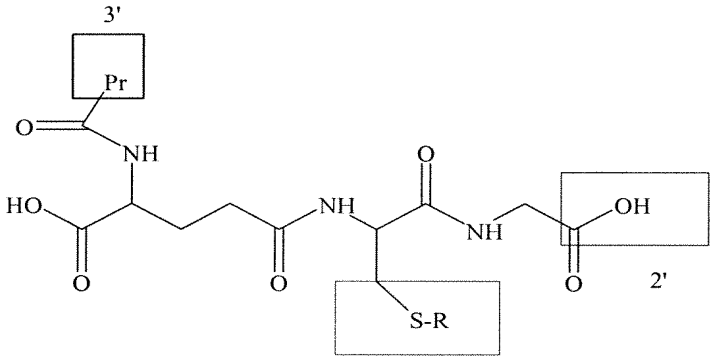
REMARKS

Claims 15 and 17-28 are pending in the application. Claims 19-22 and 24-28 have been withdrawn from the application. Therefore, claims 15, 17, 18, and 23 are at issue.

Claims 15, 17, 18, and 23 stand rejected under 35 U.S.C. §103 as being obvious over Anderson et al. U.S. Patent No. 5,464,825 ('825) in view of a McMurry publication (McMurry). The rejection is based on a combination of references wherein the '825 patent teaches alkyl monoesters of N-acyl glutathione increase intracellular GSH levels and McMurry teaches ester hydrolysis. The examiner further relies upon an "obvious to try" rationale to support the rejection. Applicants traverse this rejection.

The present invention is directed to glutathione derivatives having the structure of Compound B:

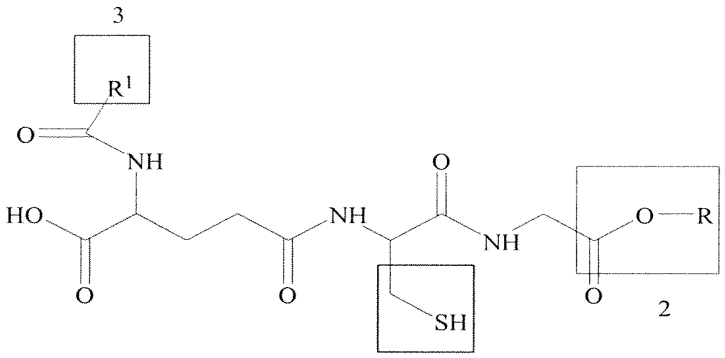


B

wherein R can be H or acetyl.

Importantly, the claimed compounds require the carboxyl group of box 2' *and* the butanoyl group of box 3'. The claimed compound B also contains a second carboxyl group.

The '825 patent discloses the following compound A:



(A)

wherein R^2 can be C_1-C_{10} alkyl, preferably C_1-C_4 alkyl, and R^1 can be C_1-C_9 alkyl, preferably C_1-C_3 alkyl. The '825 patent discloses, for example, methyl, ethyl, propyl, butyl, pentyl, and hexyl as R^1 groups.

The examiner relies upon McMurry for teaching a simple desterification reaction that would lead to the carboxyl group at position 2' of compound B, thereby rendering the present claims obvious. The examiner, however, is completely disregarding an important, and *essential*, feature of the '825 patent, *and* the unexpected benefits provided by the claimed compounds.

Compounds A and B each are N-acyl derivatives of glutathione (GSH), but compounds A and B have differences in structure with respect to the moieties in the highlighted boxes, i.e.,

(a) differences between boxes 2 and 2': present compound B has a carboxylic residue whereas '825 patent compound A has an ester residue;

(b) differences between boxes 3 and 3': present compound B has a propyl group which is a selection among all the possible residues of the '825 patent compound A; and

(c) differences between box 1 and 1': '825 patent compound A has an hydrogen residue whereas present compound B can have a hydrogen or acetyl group.

Focusing on the moieties in boxes 2 and 2', compound A of the '825 patent is an esterified derivative of claimed compound B, and a de-esterification reaction as disclosed in the McMurry publication could lead to claimed compound B. However, the cited '825 patent explicitly discourages such a de-esterification reaction to provide a compound B.

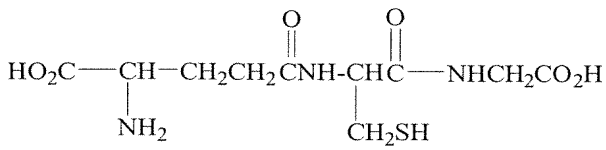
The '825 patent, at column 4, lines 17-27, provides a scheme illustrating the *in vivo*, i.e., *inside* cells (see '825 patent, column 3, lines 65-67), degradation of a compound A by de-esterification and deacylation, to provide free GSH. The '825 patent is directed to increasing intracellular levels of GSH and GSH equivalents, this is accomplished by "administering *an alkyl monoester* of N-acyl glutathione, with the esterification occurring at the glycine carboxylic group" ('825 patent, column 3, lines 21-27). Increased intracellular levels of GSH is *not* accomplished by administration of a compound having *two* carboxyl groups, as claimed and as demonstrated below.

In fact, the '825 patent teaches that the N-acetyl GSH *monoester* form is *necessary* to transport the compound into the cells, i.e., '825 patent, column 7, line 56 through column 8, line 16 stating:

> "The findings disclosed herein indicate that *the administered N-acetyl GSH monoester is transported into* the cells of the liver and kidney where it is hydrolyzed to GSH; N-acetyl GSH and GSH monoester are also formed. The studies in which mice were pretreated with L-buthionine-SR-sulfoximine provide strong evidence for the transport of N-acetyl GSH monoesters; under these conditions, the synthesis of GSH from its constituent amino acids is markedly inhibited. Also the finding of N-acetyl GSH and GSH monoester in tissues is *strong evidence that N-acetyl GSH monoester is transported into cells and hydrolyzed.* It is *also seen that intact GSH is not delivered into the cell*, since GSH synthesis is markedly inhibited by L-buthionine-SR-sulfoximine. Thus, the present method permits increasing the intracellular GSH level in instances where a deficiency of the necessary synthetase for GSH exists, or where a higher level of GSH or N-acetyl GSH is beneficial." (emphasis added)

It is important to note that "intact GSH is not delivered into the cell", and that

GSH has the structure



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which includes *two* carboxyl groups.

The present claims do not recite an ester group on the glycine residue, but require a carboxyl group. In addition, as shown above, the '825 patent discourages, and leads a person skilled in the art away from, providing a presently claimed compound having two carboxyl groups and no ester group.

It also is well known to persons skilled in the art that even a slight modification in the structure of a compound can completely change the pharmacokinetics and bioavailability of the compound. The '825 patent teaches that it is *essential* to provide the monoester compound A to effectively increase intracellular GSH levels. It cannot be predicted *a priori* that changing the ester moiety of the '825 patent to a carboxylic acid would provide a useful drug, especially in view of the teachings of the '825 patent which stresses the necessity of the monoester form of the compound.

In fact, the '825 patent demonstrates how a minor change in structure can have drastic effects on compound efficacy. The sole example of the '825 patent, i.e., N-acetyl GSH monoethyl ester, was compared to GSH for effects on glutathione levels in the liver and kidney (Example 1 and Composition Example 1 of the '825 patent). Intracellular GSH levels in the liver were *not* effected by GSH, and only a slight effect was noted in the kidneys. From the structure above, GSH contains *two* carboxylic acid groups as claimed, and a drastic difference results in intracellular GSH levels by administering GSH versus the N-acetyl GSH monoethyl ester of the '825 patent.

In summary, in addition to teaching the necessity of a monoester compound, the '825 patent shows that adverse results can result from a minor change in structure, in particular by de-esterifying the monoalkyl ester moiety. The '825 patent therefore further discourages individuals from modifying the disclosed monoester compounds in a way to

arrive the presently claimed compounds because there is no reasonable expectation of providing a compound that increases intracellular GSH levels.

It could not have been predicted that converting the ester moiety of a compound of the '825 patent to a carboxylic acid moiety would provide a compound that effectively reaches the cells where the biological action is needed. It is well known that prodrugs, like those of the '825 patent, often perform better than the corresponding drugs because they have an improved bioavailability and/or are better able to reach the intended target site.

In contrast to the teachings of the '825 patent, and unexpectedly, the glutathione derivatives of claim 15 do not require an esterified glycine residue, but perform effectively when a *second* carboxyl group is present on this residue. The glutathione derivative of claim 15 also *requires* the propyl group of box 3' to achieve the benefits of the present invention. The '825 patent provides no teaching or suggestion that a compound of the present invention having the features of boxes 1', 2', *and* 3' could enhance intracellular GSH levels, but rather shows that GSH containing two carboxyl groups did not increase intracellular GSH levels, as discussed above.

As stated above, the presently claimed compounds also do not rely solely upon a second carboxyl group on the glycine residue for enhanced activity. The propyl group of box 3' is important and necessary to achieve the enhanced activity of the present compounds. In particular, applicants have shown that an acetyl group (2 carbons) is inactive and alkanoyl groups of other lengths are of low activity or are toxic (i.e., alkanoyl groups with eight and twelve carbons). See specification, page 6, lines 14-21 and page 11, line 22 through page 12, line 15. This is unexpected and in direct contrast to the teachings of the '825 patent, wherein the carbon length of the hydrocarbon group R^1 *apparently does not effect compound activity*, and the sole example contains an acetyl group. In the '825 patent, an acetyl group at R^1 increases intracellular GSH levels. However, contrary to this teaching in the '825 patent, an acetyl group in place of a claimed butanoyl group *destroys* the activity of the present compounds. This result could not have been predicted from the teachings of the '825 patent.

With respect to the McMurry publication, this reference is merely a general teaching that esters can be hydrolyzed to acids. However, the primary '825 patent provides

no incentive for a person skilled in the art to perform such a hydrolysis. The only hydrolysis performed in the '825 patent is *in vivo*, and the '825 patent shows that de-esterification *prior* to administration provides a GSH compound that does *not* work. In particular, the '825 patent specifically teaches that the *monoester* is required to achieved the benefits of the invention and that "intact GSH" (which contains two carboxyl groups) is not delivered into the cell ('825 patent, column 8, lines 9-12). This is further demonstrated in the examples of the '825 patent, wherein glutathione, having two carboxyl groups, "had only a slight effect" ('825 patent, column 7, lines 14-19).

To support the present obviousness rejection, the examiner relies upon an "obvious to try" rationale. To reject a claim based upon this rationale, the following must be articulated:

> "(1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
>
> (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
>
> (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
>
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness."

If *any* of these findings cannot be made, then the "obvious to try" rationale cannot be used.

Applicants discussed *Takeda Chemical Industries v. Alphapharm Pty. Ltd.*, 492 F3d. 1350, 1356-7 (2007); *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.* 86 USPQ2d 1196 (Fed. Cir. 2008), and *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 87 USPQ2d 1452 (Fed. Cir. 2008) in Amendment "A" and the findings in those cases is incorporated herein by reference. In sum, the cases teach that a minor change in structure cannot support an "obvious-to-try" rationale when the prior art fails to provide a reasonable expectation of success. For the reasons stated above, the modification suggested by the examiner would not provide a reasonable expectation of increasing intracellular GSH levels.

To arrive at the present invention, a skilled artisan would have to make modifications to the '825 compounds that are neither taught nor suggested by the '825 patent, but rather are *discouraged* by the '825 patent. In particular, the '825 patent specifically teaches the need for a monoester, or else intracellular GSH levels are not increased. Accordingly, the '825 patent provides no reason for a person skilled in the art to modify a compound of the '825 patent in a way to arrive at the presently-claimed compounds.

There can be no reasonable expectation of success when the primary reference specifically shows that a compound with two carboxylic acid groups does *not* work, whereas a monoester of the compound does. The '825 patent teaches success using a monoester that is de-esterified *in vivo*. A person skilled in the art may consider using the acid form of GSH because that is the pharmaceutically-active form, but the '825 patent shows that the acid form does *not* work. For that reason, the '825 patent is directed to the mono-ester form of GSH. So where is the reasonable expectation of success by going back to the acid form (which the '825 patent discloses and shows does not work)?

In addition, if it arguably is obvious-to-try the acid form of the compound disclosed in the '825 patent, applicants further show that the *propyl group* at box 3' is *necessary* and that other chain lengths do not work. Applicants found that the N-acetyl analog of the claimed compounds *did not* perform (whereas the N-acetyl form of the '825 patent compound did perform). Only the presently claimed N-butanoyl compounds demonstrated efficacy. In contrast, the N-acetyl *monoesters* of the '825 patent (see Example) apparently perform well. These results further show how relatively minor appearing structural changes to a compound substantially alter compound efficacy, and cannot lead to a prediction of efficacy.

These findings further demonstrate the unexpected results provided by the present invention, which could not have been predicted from the disclosure of the '825 patent. The skilled person would have had *no* reasonable expectation of success from the proposed modifications that result in the claimed compounds. It is the applicants who found that the specific propyl group (box 3'), in combination with two carboxyl groups (e.g., box 2'), are able to enter cells and provide efficacious results. Varying any of these moieties will reduce or destroy these efficacious results. In particular, chains shorter or longer than propyl

shown to be either ineffective or toxic. This discovery is in direct contrast to the '825 patent, which requires a monoester and suggests that all alkyl chain lengths are effective.

With respect to the examiner's responses to applicants prior arguments, the examiner states that the '825 patent teaches monoester hydrolysis, and McMurry teaches that esters hydrolyze to carboxylic acids. This reasoning omits important aspects and disclosure of the '825 patent, i.e., the monoester is hydrolyzed *in vivo* to increase intracellular GSH levels, wherein administration of a hydrolyzed form did *not* increase intracellular GSH levels. The monoester is needed to provide efficacy, as taught by the '825 patent. The combination of references fails to provide any apparent reason to modify the compounds of the '825 patent with any reasonable expectation of providing a useful drug.

The examiner appears to require a declaration to rebut the contention of *prima facie* obviousness. However, comparing a presently claimed compound to a compound of the '825 patent would have little to no value. If one assumes that the monoester compound disclosed in the '825 patent is efficacious (as disclosed), what would this comparison show? Very little. The claimed compounds also have shown to be efficacious, and are entirely different compounds. The present invention does not reside in providing compounds better than those in the '825 patent, but resides in *different* compounds that *also* increase intracellular GSH levels, *and* wherein the presently claimed compounds have a structure that is discouraged by the '825 patent.

The '825 patent *itself* shows that a GSH derivative with two carboxylic acid groups does not work compared to the monoester. In view of the '825 patent, it is unexpected that the claimed compounds work at all.

In addition, applicants have shown that only the claimed butanoyl compound is useful. This is shown in the specification which compares compounds of different carbon lengths at the 3' position *and* having two -CO_2H groups. Therefore, the inventors *already* compared the claimed compounds to compounds *even closer in structure* (i.e., two carboxy groups and N-acyl with a chain length different from propyl) to the claimed compounds than compounds disclosed in the '825 patent (i.e., carboxy group, ester group, and N-acyl). The examiner also is directed to MPEP § 716.01(a) stating that the examiner must consider comparative data in the specification in making a conclusion of obviousness, and to *In re*

Soni. 54 F3d 746 (1995) wherein the court stated "[C]onsistent with the rule that all evidence of nonobviousness must be considered when assessing patentability, the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results." The court made it clear that such "factual evidence" in the specification must be considered and is different from "mere argument or conclusory statement" in the specification. In the case at bar, applicants have provided factual evidence comparing the claimed compounds to compounds even closer in structure to the claimed compounds than the compounds disclosed in the' 825 patent.

In summary, for all the reasons set forth above, it is submitted that claims 15, 17, 18, and 23 would not have been obvious under 35 U.S.C. §103 over a combination of the '825 patent and the McMurry publication, and that the rejection should be withdrawn. With respect to the examiner's obvious to try rationale, he has not meet his burden with respect to a reasonable expectation of success as a result of the proposed structural modification.

It is further submitted that all claims are in a form for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Dated: July 14, 2009

Respectfully submitted,

By _____

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